UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/353,126	07/14/1999	ROBERTO MALINOW	CSHL.005.01U	3018

31272 7590 02/04/2004

RAE-VENTER LAW GROUP, P.C.
P.O. BOX 1898
MONTEREY, CA 93942-1898

EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/353,126	MALINOW ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *26* is/are allowed.

6)☒ Claim(s) *1 and 3-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. **Pursuant to Interview Summaries filed on 4 September 2001, 14 January 2002, and 12 June 2003 prosecution on the merits on this instant application is hereby reopened. The finality of the last Office Action (9 May 2001) is hereby *withdrawn*. The instant Office Action is prepared in response to the Response and Amendment filed 9 November 2001.**

2. The Response and Amendments filed are hereby entered in full. Claims 1-26 are currently pending as amended on 9 November 2001.

3. All previously made Rejections and Objections are hereby *withdrawn* in view of Applicant's amendments, the long period of time passing between Office Actions, and to expedite the reopening of prosecution (MPEP §707).

Priority Claim

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120 as follows:

5. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Specification

6. The disclosure is objected to because of the following informalities: misspellings "0.fl mV" (pp. 4 line 9), "thre" (pp. 4 line 27) and unclear abbreviation "1sec" (pp. 9 line 12). Appropriate correction is required.

Drawings

7. The drawings are objected to because Figure 5 is missing. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. The Applicant is reminded to avoid the introduction of new matter (see 35 U.S.C. §112).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims **1, 3-5, 7, 8,** and **9** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *the method as claimed wherein said method is in vitro, the presenilin gene mutation is the Δ9 mutation, and is practiced to identify candidate drugs*, does not reasonably provide enablement for *practicing said method in vivo, with other presenilin*

mutations, or the identification of drugs per se. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

9. The claims are drawn very broadly to methods of identifying drugs which can be used to treat Alzheimer's disease. The language of said claims encompasses both *in vivo* and *in vitro* assays. Further the claims broadly pertain to practicing the invention in both *in vitro* and *in vivo* assays. The Examiner notes that an *in vitro* method encompasses both dissociated cells in culture and tissue slice cultures.

10. The specification teaches that mouse hippocampal cells comprising the Δ9 mutation in the presenilin gene can be used in an *in vitro* assay to identify candidate drugs for Alzheimer's disease.

11. The specification fails to provide any guidance for the successful use or sufficient disclosure of drugs for Alzheimer's disease or the practice of the claimed method *in vivo* such as in patients and non-human animal models. In addition, the claims as currently presented are drawn to a presenilin gene mutation without specifying which mutation. Since resolution of the various complications in regards to targeting the role a particular gene in an organism in Alzheimer's disease is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known Alzheimer's disease related proteins, signs, and symptoms to correlate with an alleviation of symptoms identified by practicing the

invention. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

12. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed *in vitro* screening methods to identify a drug for the treatment of Alzheimer's disease *per se* in the absence of undue experimentation. For the claimed method to identify drugs the skilled artisan must undertake the testing and evaluation of the effects of so identified drugs on Alzheimer's disease patients and/or non-human animal models.

13. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a screening method to identify drugs *in vivo* based solely on its performance *in vitro* is highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* screening assays, such a disclosure would not be considered enabling since the state of Alzheimer's disease is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

14. The following references are cited herein to illustrate the state of the art of Alzheimer's disease.

15. The term "drug" contains connotations of enablement as a substance that will have a beneficial effect on Alzheimer's disease. The method as presented and claimed does not insure that any "drug" (substance or compound) so identified will be useful for therapy. The method as supported by the Specification is in essence a screening method that allows for the identification of candidate or possible compounds which may then be further characterized and tested to determine whether or not they provide relief from Alzheimer's disease. For instance Allsop *et al.* "Modulation of β-amyloid production and fibrillization." Biochem. Soc. Symp. **67**: 1-14 teaches that Alzheimer's disease is a relentless, degenerative brain disease characterized by progressive cognitive impairment and later loss of motor skills (pp. 1). Several drug strategies are discussed by Allsop *et al.* covering strategies to prevent, delay, or reverse Aβ aggregate accumulation (senile plaques), to prevent or delay Aβ fragment production (4-10). The claims in light of the Specification do not detail which symptoms, what mechanisms, or what detrimental aspect of AD which the "drugs" identified by the method as claimed will in fact effect. Thus the skilled artisan is left no option but to undertake great and undue experimentation to first identify, then isolate or synthesize the drug, and finally conduct experiments in the absence of guidance as to what symptoms, mechanisms, or pathological aspect of AD will be delayed, prevented, reversed, or otherwise assuaged to a sufficient degree to label said compound as a "drug".

16. The claims recite a presenilin gene mutation without giving parameters for what constitutes a gene mutation which can satisfy the preamble of the claims. Lodash *et al.* (1997) "Molecular Cell Biology: Chapter 8 'Genetic Analysis in Cell Biology'" (pp. 263-303) teaches that a gene mutation includes but is not limited to a deletion, a point mutation, a substitution, an inversion, a frame-shit mutation, or a nonsense mutation. Also any given mutation can exert its

effect or not, at the level of transcription, translation, post-translation modification, in protein folding, or protein function. Thus the Specification as filed lacks sufficient disclosure to support any presenilin gene mutation other than a Δ9 mutation. And the claims as written constitute an invitation to experiment for the skilled artisan to undertake the endeavor to create, map, and characterize mutations in the presenilin gene such that they may be used in the method as claimed.

17. Further, the skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick & Fetrow (2000) "From genes to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39. For example, Jobling & Holmes (1991) "Analysis of structure and function of the B Subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that protein activity depends upon the structural characteristics (conformation) of the particular protein (amino acid sequence) affected by the mutations. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. Further it is noted, that for particularly for pathological proteins or proteins held to involved in pathogenesis of a disease, extensive and burdensome experimentation is required to confirm and characterize the role a given mutation plays. For instance, Ikeda *et al.* (December

1996) "The Clinical Phenotype of Two Missense Mutations in the Presenilin I Gene in Japanese Patients." Ann. Neurol. **40**(6): 912-917 teaches that not all presenilin-1 gene mutations vary in their effects on patients and the pathology of Alzheimer's disease (pp. 916).

18. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* screening assays to the *in vivo* practicing as exemplified in the references herein. The Examiner notes that incorporation of the suggested claim amendments at the end of this Office Action would be sufficient to obviate this enablement rejection.

19. Claims **6, 18,** and **19** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

20. The claims are drawn very broadly to methods of determining the underlying mechanism of a mutation in hippocampal cells. The language of said claims encompasses both *in vivo* and *in vitro* assays.

21. The specification teaches that mouse hippocampal cells comprising the Δ9 mutation in the presenilin gene can be used in an *in vitro* assay to identify candidate drugs for Alzheimer's disease.

22. The specification fails to provide any guidance for the successful diagnosis or assessment of the role of a mutation in $GABA_A$ receptor antagonist related pathways. Since the resolution of the various complications in regards to targeting the role a particular gene in an organism in any

given metabolic pathway is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known $GABA_A$ antagonist related activity and effects to correlate with any given mutation. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

23. Additionally, a person skilled in the art would recognize that predicting the efficacy of correlating an unspecified pathway of a $GABA_A$ receptor antagonist with an as of yet unidentified mutation based solely on prophetic nexus between a mutation in hippocampal cells as highly problematic (see MPEP §2164.01). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods to tie a given mutation in a hippocampal cell to a $GABA_A$ receptor antagonist, such a disclosure would not be considered enabling since the state of biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

24. The following references are cited herein to illustrate the state of the art of $GABA_A$ and protein biochemistry.

25. The claims recite "a common pathway with a $GABA_A$ receptor antagonist" without specifying which pathway, antagonist, or what manner in which the mutation is related to either the pathway or antagonist. Voet & Voet (1995) "Biochemistry (2nd Ed.) : Chapter 15 Introduction to Metabolism" (pp. 412-442) teach that a wide variety of pathways which differ in both nature, intermediates, and products are involved in any given hippocampal cells. Further Bradford (1986) "Chemical Neurobiology An Introduction to Neurochemistry 'Two Inhibitory Amino Acids: GABA and Glycine." (pp. 229-242) teaches that GABA is involved in a complex web of pathways including metabolic, biochemical, as well as behavioral (physological). Thus the claims as written constitute an invitation to experiment. First the skilled artisan must identify the mutation, then identify the pathway, the intermediates and products thereof, and then correlate all of the preceding with a $GABA_A$ antagonists.

26. On the amount of direction provided by the inventor, no guidance is given to which pathway is to be investigated or illuminated via practicing the invention nor is any guidance given per the nature of the pathway shared by the mutation and the $GABA_A$ receptor antagonist.

27. The Specification as written also fails to provide sufficient guidance for which $GABA_A$ receptor and which GABAA receptor antagonists. Hevers & Luddens (August 1998) "The diversity of $GABA_A$ receptors. Pharmacological and electrophysiological properties of $GABA_A$ channel subtypes." Mol Neurobiol. **18**(1): 35-86 teaches that the amino acid gamma-aminobutyric-acid (GABA) is an inhibitory neurotransmitter in the central nervous system (CNS) and mediates most of its effects through fast GABA-gated Cl^--channels ($GABA_A$). Hevers

& Luddens also teach that the art of molecular biology has uncovered a complex subunit architecture of $GABA_A$, in which a pentameric assembly derived from 5 of at least 17 mammalian subunits, grouped in the 6 classes α, β, γ, δ, σ, and ε. This variance of $GABA_A$ receptor subunit combinations permits a vast number of putative receptor isoforms. The subunit composition of a particular $GABA_A$ receptor determines the specific effects of allosterical modulators like benzodiazepines, barbiturates, steroids, some convulsants, polyvalent cations, and ethanol. Little is known about the functional properties of the β, δ, and ε subunit classes and only a few receptor subtype-specific substances like loreclezole and furosemide are known that enable the identification of defined receptor subtypes. Therefore the art teaches that GABAA receptors show structural and functional diversity as well as pharmacological diversity rendering the complexity underlying the invention as claimed.

28. The claims recite a presenilin gene mutation without giving parameters for what constitutes a gene mutation which can satisfy the preamble of the claims. Lodash *et al.* (1997) "Molecular Cell Biology: Chapter 8 'Genetic Analysis in Cell Biology'" (pp. 263-303) teaches that a gene mutation includes but is not limited to a deletion, a point mutation, a substitution, an inversion, a frame-shit mutation, or a nonsense mutation. Also any given mutation can exert its effect or not, at the level of transcription, translation, post-translation modification, in protein folding, or protein function. Thus the Specification as filed lacks sufficient disclosure to support any presenilin gene mutation other than a Δ9 mutation. And the claims as written constitute an invitation to experiment for the skilled artisan to undertake the endeavor to create, map, and characterize mutations in the presenilin gene such that they may be used in the method as claimed.

29. Further, the skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick & Fetrow (2000) "From genes to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39. For example, Jobling & Holmes (1991) "Analysis of structure and function of the B Subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that protein activity depends upon the structural characteristics (conformation) of the particular protein (amino acid sequence) affected by the mutations. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. Further it is noted, that for particularly for pathological proteins or proteins held to involved in pathogenesis of a disease, extensive and burdensome experimentation is required to confirm and characterize the role a given mutation plays. For instance, Ikeda *et al.* (December 1996) "The Clinical Phenotype of Two Missense Mutations in the Presenilin I Gene in Japanese Patients." Ann. Neurol. **40**(6): 912-917 teaches that not all presenilin-1 gene mutations vary in their effects on patients and the pathology of Alzheimer's disease (pp. 916).

30.

31. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying suggestion and

prophetic consideration to practicing the invention claimed as exemplified in the references herein.

32. Claim **13** is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *method as claimed wherein said method identifies candidate drugs*, does not reasonably provide enablement for *the identification of drugs per se*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

33. The claims are drawn very broadly to methods of identifying drugs which can be used to treat Alzheimer's disease.

34. The specification teaches that mouse hippocampal cells comprising the Δ9 mutation in the presenilin gene can be used in an *in vitro* assay to identify candidate drugs for Alzheimer's disease.

35. The specification fails to provide any guidance for the successful use or sufficient disclosure of drugs for Alzheimer's disease or the practice of the claimed method in vivo such as in patients or non-human animal models. One of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known Alzheimer's disease related proteins, signs, and symptoms to correlate with an alleviation of symptoms identified by practicing the invention. In the absence of any guidance from the specification, the amount of experimentation

would be undue, and one would have been unable to practice the invention over the scope claimed.

36. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed *in vitro* screening methods to identify a drug for the treatment of Alzheimer's disease *per se* in the absence of undue experimentation. For the claimed method to identify drugs the skilled artisan must undertake the testing and evaluation of the effects of so identified drugs on Alzheimer's disease patients and/or non-human animal models.

37. Additionally, a person skilled in the art would recognize that predicting the efficacy of using drugs identified in a screening method *in vivo* treatments for Alzheimer's disease based solely on its performance *in vitro* is highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed drugs identified in *in vivo* therapies, such a disclosure would not be considered enabling since the state of Alzheimer's disease is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

38. The following references are cited herein to illustrate the state of the art of Alzheimer's disease.

39. The term "drug" contains connotations of enablement as a substance that will have a beneficial effect on Alzheimer's disease. The method as presented and claimed does not insure that any "drug" (substance or compound) so identified will be useful for therapy. The method as supported by the Specification is in essence a screening method that allows for the identification of candidate or possible compounds which may then be further characterized and tested to determine whether or not they provide relief from Alzheimer's disease. For instance Allsop *et al.* "Modulation of β-amyloid production and fibrillization." Biochem. Soc. Symp. **67**: 1-14 teaches that Alzheimer's disease is a relentless, degenerative brain disease characterized by progressive cognitive impairment and later loss of motor skills (pp. 1). Several drug strategies are discussed by Allsop *et al.* covering strategies to prevent, delay, or reverse Aβ aggregate accumulation (senile plaques), to prevent or delay Aβ fragment production (4-10). The claims in light of the Specification do not detail which symptoms, what mechanisms, or what detrimental aspect of AD which the "drugs" identified by the method as claimed will in fact effect. Thus the skilled artisan is left no option but to undertake great and undue experimentation to first identify, then isolate or synthesize the drug, and finally conduct experiments in the absence of guidance as to what symptoms, mechanisms, or pathological aspect of AD will be delayed, prevented, reversed, or otherwise assuaged to a sufficient degree to label said compound as a "drug".

40. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* screening assays to the *in vivo* treatment of Alzheimer's disease using drugs so identified as exemplified in the references herein. The Examiner notes that incorporation of the suggested

claim amendments at the end of this Office Action would be sufficient to obviate this enablement rejection.

41. Claims **14-17, 20,** and **21** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *method as claimed wherein said method is in vitro and is practiced to identify candidate drugs*, does not reasonably provide enablement for *practicing said method in vivo or the identification of drugs per se.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

42. The claims are drawn very broadly to methods of identifying drugs which can be used to treat Alzheimer's disease. The language of said claims encompasses both *in vivo* and *in vitro* assays. Further the claims broadly pertain to practicing the invention in both in vitro and in vivo assays. The Examiner notes that an *in vitro* method encompasses both dissociated cells in culture and tissue slice cultures.

43. The specification teaches that mouse hippocampal cells comprising the Δ9 mutation in the presenilin gene can be used in an *in vitro* assay to identify candidate drugs for Alzheimer's disease.

44. The specification fails to provide any guidance for the successful use or sufficient disclosure of drugs for Alzheimer's disease or the practice of the claimed method *in vivo* such as in patients or non-human animal models. One of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the

quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known Alzheimer's disease related proteins, signs, and symptoms to correlate with an alleviation of symptoms identified by practicing the invention. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

45. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed *in vitro* screening methods to identify a drug for the treatment of Alzheimer's disease *per se* in the absence of undue experimentation. For the claimed method to identify drugs the skilled artisan must undertake the testing and evaluation of the effects of so identified drugs on Alzheimer's disease patients and/or non-human animal models.

46. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a screening method to identify drugs *in vivo* based solely on its performance *in vitro* is highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* screening assays, such a disclosure would not be considered enabling since the state of Alzheimer's disease is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

47. The following references are cited herein to illustrate the state of the art of Alzheimer's disease.

48. The term "drug" contains connotations of enablement as a substance that will have a beneficial effect on Alzheimer's disease. The method as presented and claimed does not insure that any "drug" (substance or compound) so identified will be useful for therapy. The method as supported by the Specification is in essence a screening method that allows for the identification of candidate or possible compounds which may then be further characterized and tested to determine whether or not they provide relief from Alzheimer's disease. For instance Allsop *et al.* "Modulation of β-amyloid production and fibrillization." Biochem. Soc. Symp. **67**: 1-14 teaches that Alzheimer's disease is a relentless, degenerative brain disease characterized by progressive cognitive impairment and later loss of motor skills (pp. 1). Several drug strategies are discussed by Allsop *et al.* covering strategies to prevent, delay, or reverse Aβ aggregate accumulation (senile plaques), to prevent or delay Aβ fragment production (4-10). The claims in light of the Specification do not detail which symptoms, what mechanisms, or what detrimental aspect of AD which the "drugs" identified by the method as claimed will in fact effect. Thus the skilled artisan is left no option but to undertake great and undue experimentation to first identify, then isolate or synthesize the drug, and finally conduct experiments in the absence of guidance as to what symptoms, mechanisms, or pathological aspect of AD will be delayed, prevented, reversed, or otherwise assuaged to a sufficient degree to label said compound as á "drug".

49. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* screening assays to the *in vivo* practicing as exemplified in the references herein. The Examiner notes that incorporation of the suggested claim amendments at the end of this Office Action would be sufficient to obviate this enablement rejection.

50. Claims **1, 2-5, 7-9, 13-17, 20,** and **21** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

51. Claims 1, 5, 8, 9, 13, 14, 17, 20, and 21 recite "drug" while not demonstrating or disclosing any compound, substance, and/or agent that actually has a salubrious effect on Alzheimer's disease thus implying that the therapeutic value of said "drug" is presumed or not known and must be confirmed. Thus, the claims are drawn to a genus of agents that is defined by desired activity.

52. Claims 1, 5, 8, and 9 recite "a presenilin gene mutation" while not demonstrating or disclosing any mutation other than the Δ9 mutation. Thus said gene mutation is not adequately described such that its nature may be known. Thus, the claims are drawn to a genus of mutations that is defined by desired activity (or inactivity) of presenilin.

53. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or

chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of a desired activity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

54. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

55. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003). In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using unspecified compound, in order to relieve pain

without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since patent described the compound's desired function of reducing activity of enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to discover those with desired effect, but patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound, since specification did not indicate that compounds are available in public depository, since claimed treatment method cannot be practiced without compound, and since inventors thus cannot be said to have "possessed" claimed invention without knowing of compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

56. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision. The Examiner also notes that Applicant may obviate this written description rejection by amending claims to read "candidate drug" in the preamble and adding "wherein said presenilin gene mutation is Δ9" to claim 1.

57. Claims **10-12** and **22-25** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

58. Claim 10 recites "a candidate drug that is not an antibody" while not disclosing or teaching, implicitly or explicitly, what is the nature and structure of such a drug. Nor does the specification provide defining characteristics as to what make a drug a candidate thus implying that the structure and activity of the drug used is not known or must be confirmed.

59. Claims 22 and 24 recite "a candidate drug that suppresses intracellular calcium rise" while not disclosing or teaching, implicitly or explicitly, what is the nature and structure of such a drug. Nor does the specification provide defining characteristics as to what makes a drug a candidate thus implying that the structure and activity of the drug used is not known or must be confirmed. Thus, the claims are drawn to a genus of agents that is first defined by novelty as well as a desired activity.

60. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of novelty and/or a desired activity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described.

Accordingly, the specification does not provide adequate written description of the claimed genus.

61. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

62. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003). In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since patent described the compound's desired function of reducing activity of enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to discover those with desired effect, but patent did not name even one compound that assays would

identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound, since specification did not indicate that compounds are available in public depository, since claimed treatment method cannot be practiced without compound, and since inventors thus cannot be said to have "possessed" claimed invention without knowing of compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

63. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

64. Claims **1, 2-5, 7-9, 10, 11, 13-17, 20,** and **21** are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the testing and confirmation of the drugs identified by the screening method as "drugs" *per se.*

65. Claims **6, 18,** and **19** are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: how the mutation must effect the pathway such that it can be said to be in common with a $GABA_A$ receptor antagonist.

Summary

66. Claims **1** and **3-25** are hereby rejected.

67. Claim **26** is allowable over the prior art.

68. The following claims drafted by the examiner and considered to distinguish patentably over the art of record in this application, are presented to applicant for consideration:

Claims 1-12 (Cancelled)

Claim 13 (Currently Amended) An in vitro method for screening for candidate drugs for the treatment of Alzheimer's disease, said method comprising:

contacting slices of mouse hippocampal tissue containing cells, having a PS-1 Δ9 mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells to tetanic stimulation; and

determining the effect of said candidate drug on the synaptic potentiation of said mutant hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

Claim 14 (Currently Amended) An in vitro method for screening for candidate drugs for the treatment of Alzheimer's disease, said method comprising:

contacting mammalian hippocampal cells comprising a PS-1 Δ9 presenilin gene mutation wherein said hippocampal cells have enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells to tetanic stimulation; and

determining the effect of said candidate drug on the synaptic potentiation of said mutant hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

Claim 15 (Reiterated) The method according to Claim 14, wherein mouse hippocampal tissue slices comprise said mutant hippocampal cells.

Claim 16 (Reiterated) The method according to Claim 14, wherein said enhanced synaptic potentiation is a result of a change in the $GABA_A$ receptor pathway.

Claim 17 (Currently Amended) An in vitro method for screening for candidate drugs for the treatment of Alzheimer's disease, said method comprising:

contacting mammalian hippocampal cells comprising a PS-1 Δ9 presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to a tetanic stimulus;

measuring changes in potentiation with time of the mutant hippocampal cells and wild-type hippocampal cells and comparing the effect of said candidate drug on the synaptic

potentiation of said mutant hippocampal cells as compared to the observed synaptic potentiation of said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells as compared to the synaptic potentiation of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

Claims 18-19 (Cancelled)

Claim 20 (Currently Amended) An in vitro method for screening for candidate drugs for the treatment of Alzheimer's disease, said method comprising:

contacting mammalian hippocampal cells comprising a PS-1 Δ9 presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to a tetanic stimulus at a first potential of glutamate currents and a second potential of $GABA_A$ currents;

measuring the synaptic response at each of the first and second potentials for said mutant hippocampal cells and said wild-type hippocampal cells and comparing the effect of said candidate drug on said mutant hippocampal cells and said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic response of the mutant hippocampal cells without a significant change in the synaptic response of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

Claim 21 (Currently Amended) An in vitro method for screening for candidate drugs for the treatment of Alzheimer's disease, said method comprising:

contacting mouse hippocampal cells comprising a PS-1 Δ9 presenilin-1 gene mutation and having enhanced synaptic potentiation upon tetanic stimulation as compared to wild-type hippocampal cells, with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to tetanic stimulus; and

comparing the effect of said candidate drug on said mutant hippocampal cells and said wild-type hippocampal cells upon tetanic stimulation;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells without a significant change in the synaptic potentiation of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

Claims 22-25 (Cancelled)

Claim 26 (Reiterated) A method for screening for a candidate drug that suppresses intracellular calcium rise in slices of mouse hippocampal tissue containing cells having a PS-1 Δ9 mutation in a presenilin gene combined with a candidate drug for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug that suppresses intracellular calcium rise in said cells;

subjecting said mutant hippocampal cells to tetanic stimulation; and

determining the effect of said candidate drug on the ratio of peak inhibitory to excitory responses;

wherein an enhanced said ratio of peak inhibitory to excitory responses in said mutant hippocampal cells as compared to wild-type hippocampal cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
January 29, 2004

Gary L. Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600